

SYNTHESIS AND CHARACTERIZATION
OF PYRIDINE AND 2,6-DIPHENYL-PYRIDINE ETHERS

Leonard L. Matz
Independent
3061 Bishop Road
Appleton, NY 14008

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INTRODUCTION

Three novel pyridine ethers have been synthesized for extension of studies on coal systems¹. Past studies have revealed that hydrogen bonding activates alkyl-aryl ethers toward cleavage by iodide ion in pyridine involving hydrogen bonding to coal². Pyridine ethers have been synthesized *de novo* from 2,6-diphenyl-1,3,5-pentanetrione which had also been synthesized *de novo* from 1-phenyl-1,3-butanedione after formation of its mono-then di-anion and combination with methyl benzoate^{3,4}. These reactions seem to provide good yields because of the driving force of the charged molecular species. Coal is now thought to be as elastomer in which strong internal hydrogen bonding gives it high glass transition temperatures. The same acidic hydrogen donors and basic hydrogen receptors that provide strong hydrogen bonds in the bulk structure populate the surface of coal powders⁵. As in experiments using 1,3-dimethylnaphthalene and decalin⁶, solvation properties of the pyridine ethers will be tested on coal fractions in contemplated experiments.

RESULTS

1,5-Diphenyl-1,3,5-pentanetrione The enolate carbanion of 1-phenyl-1,3-butanedione was obtained by proton extraction with sodium hydride in the aprotic solvent, 1,2-dimethoxy ethane (monoglyme). Condensation of this carbanion with methyl benzoate yielded the triketone, 1,5-diphenyl-1,3,5-pentanetrione. This arylation apparently involves the di-anion of the β -diketone which is formed in a step-wise extraction of its α -hydrogens. The terminal α -hydrogen is not the first extracted from the β -diketone, but is only extracted after mono-anion formation and in the presence of methyl benzoate. The terminal α -hydrogen is, however, the site of reaction of the β -diketone with the carbonyl carbon of the ester. The methoxide group of the ester neutralized by the Na^+ counter ions, then leaves the condensation product. Exposure to air with its incipient moisture and neutralization of the reaction mixture with 6N HCl provide the protons for neutralization of the carbanions present and formation of the triketone.

This reaction occurs with a high degree of efficiency since 86.9% yields could be obtained (See Table 1).

Apparently once formed, the di-anion is quite reactive and the

reaction is evidently specific for the terminal carbon of the dianion. As expected, the symmetric triketone formed was soluble in diethyl ether, but its solubility varied considerably depending on the pH of the reaction mixture (Table 2)

These differences could be a reflection of minor changes in the structure of the triketone. Variation of the color, crystalline form and melting points of triketone which substantiate similar earlier observations are also suggestive of small variations in the structure of the triketone. Because of the H-bonding, various keto-enol tautomeric forms can be envisioned and as pH changes occur in the solvent all of these forms are undoubtedly present in the solution. At low pH values the triketone is probably found as a doubly H-bonded enolic structure (Formula 1), at intermediate pH values as a mono-H-bonded structure (Formula 2) and at high pH values as a keto form (Formula 3) with little H-bonding (Fig. 2).

2,6-Diphenyl-4(1H)-pyridinone This pyridinone was produced by the cyclization of the 1,5-diphenyl-1,3,5-pentanetrione with liquid ammonia. Because of the high pH of the reaction milieu, which causes the enolization of the ketone groups, the addition product is the primary amine-enol or dienol intermediate.

Cyclization by addition of the primary amine to the other terminal carbon of the pentanetrione chain then readily occurs. This di- or trienolic structure is then dehydrated to form the highly conjugated diphenylpyridine derivative with its quinoid-like pyridine ring.

The synthesized pyridinone possessed the literature values of the physical properties. In addition, the physical properties of the triketone and pyran were considerably different. These results suggest because of their interdependence that the structural parameters attributed to these isolates are consistent and reputable.

DISCUSSION

As expected the product, 1,5-diphenyl-1,3,5-pentanetrione, is formed with a high degree of efficiency (86.9% yields). Although the symmetric triketone was soluble in diethyl ether, variations of the pH of the reaction mixture produced slight variations in the structure of the triketone and therefore variation of the color, crystalline form and melting points of triketone products. Because of the H-bonding, various keto-enol tautomeric forms can be envisioned and as pH changes occur in the solvent all of these forms are undoubtedly present in the reaction milieu.

The ultrastructure of coals is susceptible to study using small molecular weight organic molecules which are not susceptible to alteration by the interior of the coal pores. We have chosen to use the commonly accepted organic molecules which are very resistant to alteration in such an organic milieu- ethers. Theoretically these molecules can be used as molecular sieves to approximate the size of coal pores⁷. Unfortunately, the ethers which we have used have

proven to be unreasonable solvents since they react with the coal ultrastructure.

Another problem in interpretation occurs because of the interaction of the pyridine ethers with the coal structure⁸. For example, the results of the study involving the use of 4-methylpyridine reported above.

SUMMARY

1-Hydrogen bonding is a significant interference in the synthesis of 2,6-diphenyl-1,3,5-pentanetrione, yet yields of 90+% prove this specific synthesis effective.

2-Because of the very prominent unsaturation of the products of this synthesis-the product compounds are very colorful.

3-These ethers cannot be considered inert and make interpretation of these results difficult.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Thomas Hoover Capillary Melting Point Apparatus (Uni-melt) and observed at a rate of 2°C/min. 1H-NMR Spectra were measured on a Varian T-60 Nuclear Magnetic Resonance Spectrometer using tetramethylsilane (TMS) as an internal standard. The solvents used were either chloroform-d or acetone-d₆. Infrared spectra were recorded on a Perkin-Elmer 337 grating Spectrophotometer with calibration peaks at 1601 and 907 cm⁻¹. Mass spectral analysis was conducted on a Dupont 21-490 Mass Spectrometer. TLC was performed on precoated Silica Gel 60F-254 plates (Merck, Darmstadt, 0.25 mm thickness). HPLC analysis was carried out on a Model 342 Gradient Liquid Chromatograph system, retention times and area measurements were recorded by a Shimadzu Chromatopac C-R1B. The column used for the HPLC was 4.6 mm x 25 cm CB reverse phase. Pre-injection clean up of HPLC samples included centrifugation in a Beckman Microfuge TM 11 at 11,000 rpm. Organic solids were dried under vacuum for at least 2 h over CaSO₄ before analysis.

Preparation Of 1,5-diphenyl-1,3,5-pentanetrione^{3,4} Sodium hydride (36.99 g/1.54 moles in a 60% mineral oil dispersion) was added to 100 mls of dried 1,2-dimethoxyethane under a blanket of anhydrous nitrogen. After stirring for 15 m at room temperature the glyme which contained mineral oil and suspended fines was removed, discarded and replaced at least three times to insure removal of the mineral oil after addition of 200-300 ml of glyme. The slurry was then heated to reflux and the 1-phenyl-1,3-butanedione (50.00 g/0.31 moles) in 150 mls of solvent was added dropwise (over 30-60 m) from an addition funnel. After 45 m from completion of the addition, a solution of methyl benzoate (50.32 g/0.37 moles) in 100 ml of glyme was added dropwise. The reaction mixture was then heated at reflux for 4-8 h. After equilibration with the atmosphere and cooling, the reaction mixture which was usually

thick and crusty, was resuspended with additional glyme, if necessary, stirred and adjusted to pH=6 with concentrated HCl. The glyme was then removed in a rotary evaporator. The tar-like residue was extracted with diethyl ether, and the yellow-brown ethereal solution was dried over anhydrous Na_2SO_4 . After removal of most of the ether, the crude 1,5-diphenyl-1,3, 5-pentanetrione was recrystallized from the residue with 95% ethanol as yellow-brown crystals to give 47.33 g (57.7% Yd.): mp 107.0-109.0°C, (lit., 106-109°C)¹; NMR (CDCl_3): δ = 11.8-12.0 (d, 1), 7.8-8.0 (m, 6), 7.4-7.6 (m, 7), 6.0 (s, 1); IR (KBr): 3450, 3150, 2950, 2880, 1630, 1590, 1500, 1400, 1300, 1290, 1170, 900, 780, 690 cm^{-1} ; Mass Spectrum, m/e : 266, 105.

*Preparation of 2,6-diphenyl-4(1H)-pyridinone*³ 1,5-diphenyl-1,3,5-pentanetrione (43.95 g/0.17 moles) was dissolved in 200 ml of anhydrous ethanol. Commercial anhydrous liquid ammonia was then bubbled through the mechanically stirred slurry until the solution became dark brown and the reaction mixture cooled to room temperature. The solution was then taken to dryness by heating in an open round bottom flask at 90-100°C until a brownish tar remained. This procedure was then repeated and slightly modified by the addition of 50 g of anhydrous Na_2SO_4 before the final evaporation. Recrystallization is accomplished directly from the residue with benzene. After drying 27.21 g (66.6% yield) of a white powder was isolated and identified as 2,6-diphenyl-4(1H)-pyridinone: mp 176-179°C (lit., 176-179°C²); NMR (CD_3COCD_3): δ = 8.0-8.3 (m, 7), 7.3-7.4 (m, 7), 7.2 (s, 1); IR (KBr): 3450, 3150, 3080, 2950, 2825, 1640, 1600, 1550, 1260, 975, 950, 780, 705, 555; Mass Spectrum (m/e): 247, 247.

*Preparation of 4-methoxypyridine*⁷. To 10 ml of dried methanol were added 1.7 g/0.074 moles of metallic sodium. After disappearance of the sodium and cessation of H_2 evolution, 5.00 g/0.033 moles of dried 4-chloropyridine hydrochloride (Aldrich) dissolved in 30 ml of dried methanol were added dropwise over 2 h. The reaction mixture was then heated at reflux for 7 days. TLC revealed only trace amounts of 4-chloropyridine and the 4-methoxypyridine (Yd. = 2.80 g/0.026 moles, 76.9%) was isolated by vacuum distillation: bp 152-154°C (=400 torr) or 41-45°C (0.7-0.8 mm) [lit., 95-96°C at 31 mm⁵ or 190.5-191.0°C (738.3 mm)⁴]; NMR (CD_3COCD_3): δ = 8.4-8.6 (d, 4), 6.7-6.9 (d, 4), 3.8 (s, 1); IR (KBr): 3450, 3050, 2990, 2960, 2860, 1600, 1460, 1440, 1295, 1220, 1035, 828, 820, 540, cm^{-1} ; Mass Spect (m/e): 109.

*Preparation of 4-phenoxy pyridine*⁸. Phenol (12.44 g/0.073 moles) was dissolved in dried toluene under a blanket of anhydrous nitrogen (Fig. 5). Metallic sodium (3.04 g/0.132 moles) was then slowly added to the stirred reaction mixture. After 1 h 4-chloropyridine-hydrochloride (6.61 g/0.044 moles) was slowly added through one side neck of the three neck flask. This caused formation of H_2 and care was taken to control the reaction. After addition of the hydrochloric acid salt, the reaction was heated at reflux for 10 days. At this time, TLC revealed only trace amounts

of remaining reactant. Work up involved¹⁴ neutralization of the reaction mixture to pH=7 followed by steam distillation of the reaction mixture. The distillate was extracted with liberal quantities of diethyl ether, the ethereal extracts were dried with Na₂SO₄ and the diethyl ether partially removed in a rotary evaporator. Vacuum distillation of the remaining extract gave 3.2 g of 4-phenoxy pyridine (35.1 % Yd.): bp 78-79 (50 ul) [lit., 134-136 (10 mu)¹²; NMR (CD₃Cl) δ : 8.2-8.4 (d, 2), 7.0-7.4 (m, 10), 6.8-7.0 (m, 6); IR(neat): 3007, 3005, 2950, 2850, 2730, 2620, 2500, 1595, 1500, 1270, 1220, 886, 760, 700, 632 cm⁻¹; Mass Spect (m/e): 206.

Preparation of 2,6-diphenyl-4-chloropyridine¹² 2,6-diphenyl-4(1H)-pyridinone (12.17 g/0.049 moles) and phosphorus pentachloride (30.75 g/0.993 moles) were mixed under nitrogen and moistened with dry phosphorus oxychloride (8 ml)(Fig. 5). While heating to 150°C for 2 h the liquid milieu progressed from a cloudy white to clear red appearance. The phosphorus oxychloride was then removed by distillation and the melt poured into cold water. After stirring the cooled suspension until the viscous reaction mixture became a flocculent precipitate, the precipitate was collected on a Buchler funnel. 10.50 g (86.3% Yd.) of 2,6-diphenyl-4-chloropyridine was recrystallized from the precipitate with 95% ethanol: mp 83-84°C (lit., 72)¹⁰; NMR (CDCl₃) δ : 7.9-8.2 (m, 8), 7.6 (s, 1), 7.3-7.5 (m, 9) or NMR (CD₃COCD₃) δ : 8.0-8.4 (m, 8), 7.8 (s, 1), 7.4-7.6 (m, 9); IR (KBr): 3450, 3150, 1570, 1420, 1240, 865, 770, 735, 690 cm⁻¹; Mass Spect (m/e) 265.

Preparation of 2,6-diphenyl-4-methoxypyridine¹⁰ Metallic sodium (0.65 g/0.028 moles) was added slowly and carefully to 10 ml of dried methanol in a three neck reaction vessel(Fig. 5). After disappearance of the sodium and abatement of H₂ evolution, the solution was refluxed for 1 hr. After cooling, 2.15 g/0.094 moles of 2,6-diphenyl-4-chloropyridine dissolved in 15 mL of dried methanol was added to the reaction vessel. The temperature was again raised to reflux of the reaction mixture. After 6 days HPLC revealed that 50% of the 2,6-diphenylpyridine was 2,6-diphenyl-4-chloropyridine and 50% was 2,6-diphenyl-4-methoxypyridine. Therefore, 0.65 g/0.028 moles in 10 mL of dried methanol was again added to the reaction mixture. After refluxing for four more days, the reaction mixture was then poured into ice water and the aqueous solution extracted several times with diethyl ether. The ether extracts were then combined and concentrated to give 1.83 g/0.007 moles of impure 2,6-diphenyl-4-methylpyridine. Recrystallization was accomplished with absolute methanol giving 1.14 g/0.004 moles of 2,6-diphenyl-4-methoxypyridine (46.3 %Yd.): mp 79-80°C (lit., 79-80°C)⁵; NMR (CDCl₃) δ : 8.0-8.2 (m, 4), 7.3-7.6 (m, 8), 7.1 (s, 1), 3.8 (s, 1); IR (KBr): 3050, 2850, 2000, 1550, 1400, 1350, 1210, 1070, 1020, 895, 860, 835, 770, 690, 630 cm⁻¹; Mass Spect (m/e) 261.

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TABLE

Table 1. Physical Properties of Synthetically Prepared Precursors and Ethers

Table 2. Physical Properties of 1,5-Diphenyl-1,3,5-pentanetrione

a-Moles 1-diphenyl-1,3-butanedione:mole NaH:moles methyl formate

b-Solvent not dried immediately before synthesis

c-Only one crystallization, second was usually not fruitful

Figures

Name	Recrystallization Solvent	Color	Mp (Bp)	% Yd
1,5-Diphenyl-1,3,5-pentanetrione	95% Ethanol	Yellow	107-109	57.7
2,6-Diphenyl-4(1H)-pyridinone	Benzene	Cream	176-179	66.6
2,6-Diphenyl-4H-pyran-4-one	Ethanol-Water	White	137-139	79.8
2,6-Diphenyl-4-chloropyridine	95% Ethanol	White	83-84	86.3
2,6-Diphenyl-4-methoxypyridine	Methanol	White	79-80	46.3
4-Methoxypyridine	Distilled Water	Clear	41-45	
4-Phenoxypyridine	Distilled Water	Clear	78-79	

Preparations	Mole Ratio ^a	Solvent (Recrys.)	Color	%Yd.	mp
F-1A	1-3.3-1	95% EtOH	brown	58.6	106-108
P-2A	1-4.2-1.2	95% EtOH	lime-yellow	86.9	108-110
P-2B	1-4.2-1.2	95% EtOH	lime-yellow	86.9	108-110
P-21A	1-4-1.2	95% EtOH	lime-yellow	— ^b	107.5-110
P-21B	1-4-1.2	95% EtOH Hexane Cyclohexane	browns	—	113-122
P-29A	1-5-1.2	95% EtOH	brown	57.7	107-109
P-29A-A	1-5-1.2	95% EtOH Hexane Cyclohexane	brown	57.7	106-108
P-29B	1-5-1.2	95% EtOH	brown	57.7	107-109
P-III-1-A	1-4-1	95% EtOH	brown	38.0 ^c	105-108

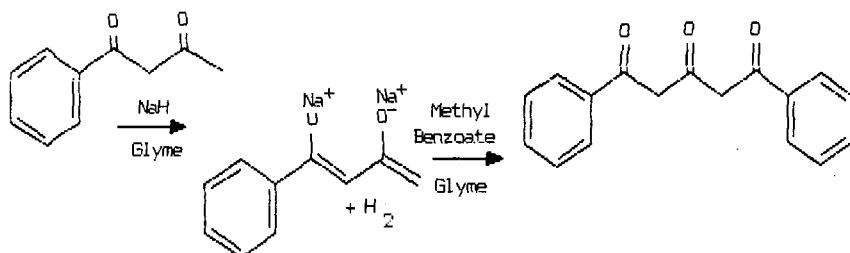


Fig. 1. Synthesis of 1,5-Diphenyl-1,3,5-pentanetrione

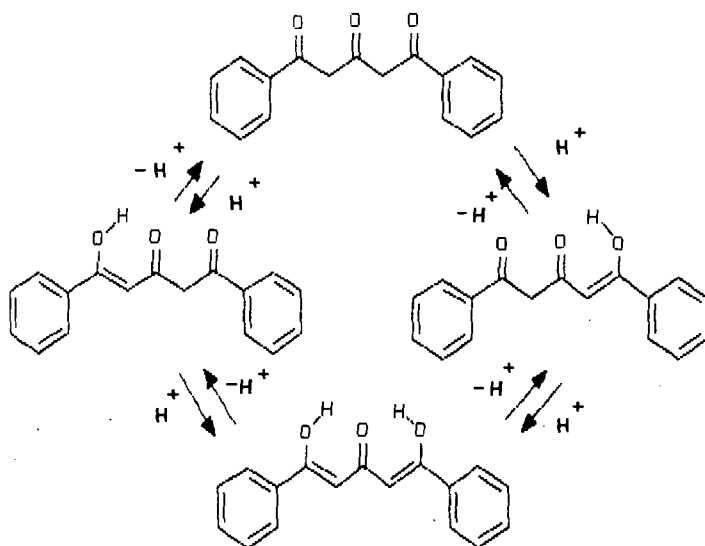


Fig. 2. Hydrogen Bonding of 2,6-Diphenyl-1,3,5-pentanetrione

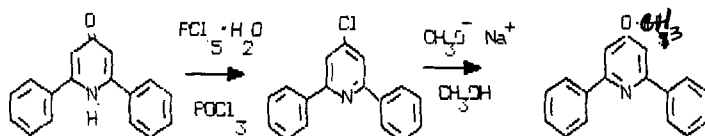


Fig. 3. Synthesis of 2,6-Diphenyl-4-methoxypyridine